SARCOMA FOUNDATION of AMERICA
We envision a world where no one dies from sarcoma.

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VIA ELECTRONIC DELIVERY

October 20, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852.

RE: Guidance for Industry (Draft): Approaches to Assessment of Overall Survival in Oncology Clinical Trials
Docket ID: FDA-2024-D-5850

The Sarcoma Foundation of America (SFA) appreciates the opportunity to provide comments and recommendations on the Food and Drug Administration's (FDA's) Draft Guidance for Industry entitled "Approaches to Assessment of Overall Survival in Oncology Clinical Trials."

SFA was founded in 2000 to amplify the voice of the sarcoma community and advocate on behalf of all people affected by sarcoma. SFA's mission is to improve outcomes for people diagnosed with sarcoma by funding and advancing research, educating and providing resources for people diagnosed with sarcoma, advocating on behalf of the community, bringing together the collective sarcoma voice, and growing awareness about the disease.

We are the largest private funder of research in the sarcoma community and have invested over $27 million in sarcoma research. We are also the largest patient advocacy organization representing all sarcoma patients regardless of subtype. SFA is, therefore, committed to ensuring that FDA initiatives, policies and process refinements facilitate the innovation needed to address the significant unmet needs within our communities. Our comments provide background outlining the challenges associated with research and development efforts in sarcoma and urge FDA to:

1) Acknowledge that overall survival as an efficacy endpoint is unlikely to sufficiently "mature" data to reliably inform regulatory decisions in rare, heterogeneous cancers such as sarcoma.
2) Harmonize the draft guidance with prior (final) guidance on multiple endpoints.[1]
3) Clarify expectations for crossover in ethically sensitive settings.
4) Incorporate into its guidance a recommendation for sponsors to include patient-centered endpoints that can signal treatment benefit and harms.

[1] Food and Drug Administration. (2022). Multiple Endpoints in Clinical Trials, Guidance for Industry

Finally, and perhaps most importantly, we have significant concerns that any one-size-fits-all policy on clinical trial design tends to ignore the mathematical realities associated with sarcoma and other rare and ultra-rare, heterogenous cancers. The preference for randomized controlled trials (RCTs), for example, does not recognize that randomization can be a poor mechanism for controlling heterogeneity across patients and disease subtypes unless the study population is sufficient to counter that "noise." When these studies fail, patients and clinicians are left with uncertainties on whether the failure was due to the treatment or the study design. For our patient communities, the stakes are too high, and treatment options are too few to pin hopes on study designs and endpoints that are not fit-for-purpose.

As more fully detailed below, SFA strongly believes that overall survival as an efficacy endpoint in sarcoma studies will further complicate research and inject additional uncertainties in data interpretation.

Background

Sarcoma is a rare cancer with over 100 subtypes (as classified by the World Health Organization (WHO)) that together account for just 1% of all adult cancers and 21% of childhood cancers.[2] [3]In the U.S., an estimated 17,000 people are diagnosed with sarcoma each year in the United States - approximately 4,000 bone sarcomas and 13,000 soft tissue sarcomas.[4] For some sarcoma patients, surgical interventions may be curative either alone or in combination with chemotherapy and/or radiation. Patients with nonresectable tumors or refractory/recurrent disease rely on systemic therapy regimens to improve survival and maintain quality of life. Unfortunately, many sarcoma subtypes remain without an FDA-approved, on-label treatment option.

SFA understands that multiple, interlocking challenges complicate the FDA approval process for sarcoma treatments, largely due to the cancers' rarity and diverse subtypes. These challenges impact clinical trial design, patient recruitment and the commercial feasibility of drug development efforts,[5] [6] and include:

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[2] Soupir, A., Ospina, O.E., Hampton, O. *et al.* Genomic, transcriptomic, and immunogenomic landscape of over 1300 sarcomas of diverse histology subtypes. *Nat Commun* **16**, 4206 (2025). https://doi.org/10.1038/s41467-025-58678-6

[3] Sarcoma Study - NCI

[4] 2025 Sarcoma Statistics - SFA

[5] Taking on the challenge of treating sarcomas

[6] Stacchiotti S, et al., How to foster new treatment development in ultra-rare tumours? Joint EMA-EORTC multi-stakeholder workshops on ultra-rare sarcomas as a model for rare cancers, Cancer Treatment Reviews, Volume 140,2025,103003,ISSN 0305-7372,https://doi.org/10.1016/j.ctrv.2025.103003. (https://www.sciencedirect.com/science/article/pii/S0305737225001252)

- **Rarity and heterogeneity:**[7] The extreme diversity in sarcoma subtypes means a treatment that works for one subtype may be ineffective for another, complicating the design of a single trial addressing multiple subtypes and limiting the opportunity for return on investment for a drug labeled for a single, very rare sarcoma.

- **Trial design limitations:** The traditional clinical trial model, which studies one regimen for one type of cancer, is often insufficient for rare cancers like sarcoma. Randomized controlled trials, however, present significant risk and uncertainty due to heterogeneity in prognosis, disease progression and, potentially, response to therapy.
    - Alternative approaches, such as "master protocols" (basket, umbrella, and platform trials) or Bayesian models are more likely to be "fit for purpose,"[8] but there is no clear understanding of how and whether FDA would accept these study designs.

- **Navigating expedited pathways:** While the FDA offers expedited pathways like accelerated approval, there is a risk that a confirmatory RCT with an overall survival endpoint would be required. This was the case with olaratumab.[9] Failure to demonstrate an overall survival benefit across multiple sarcoma subtypes through 110 sites in 25 countries led to the drug's withdrawal.[10]

- **Expertise and access to care:** The best outcomes for sarcoma patients often require a multidisciplinary team within a sarcoma treatment center.[11] Many patients seeking to enroll in a clinical trial do not have access to this expertise, leading to increased heterogeneity even when a single sarcoma subtype is studied.[12]

Recommendations

(1) SFA urges FDA to acknowledge that overall survival as an efficacy endpoint is unlikely to yield sufficiently "mature" data to reliably inform regulatory decisions in rare, heterogeneous cancers such as sarcoma.

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[7] Id.
[8] The traditional clinical trial model, which studies one regimen for one type of cancer, is often insufficient for rare cancers like sarcoma.
[9] Olaratumab (LARTRUVO) | FDA
[10] Eli Lilly pulls Lartruvo from market in wake of failure to confirm survival benefit in soft tissue sarcoma | FirstWord Pharma
[11] Hollenquest, B., Montgomery, K., Lucy, A., Banks, A., Eulo, V. and Broman, K. (2025), Effect of a Multidisciplinary Clinic on Time to Treatment for Soft Tissue Sarcoma. Journal of Surgical Oncology, 132: 763-772. https://doi.org/10.1002/jso.70061
[12] Blay, JY, et al., Improved survival using specialized multidisciplinary board in sarcoma patients, Annals of Oncology, Volume 28, Issue 11,2017,Pages 2852-2859, ISSN 0923-7534, https://doi.org/10.1093/annonc/mdx484. https://www.sciencedirect.com/science/article/pii/S0923753419346046

We appreciate FDA's draft guidance emphasizing the assessment of overall survival (OS) to ensure that treatments demonstrating a clinical benefit such as improvements in progression free survival (PFS) are not associated with longer-term harms. We expect that FDA's goals of ensuring that cancer treatments are safe and effective through clinical studies with an OS endpoint can be met if there is a sufficient patient population and homogeneity in disease course to power the study. That has not been the case for most FDA-approved treatments in sarcoma.

Extreme heterogeneity and rarity complicate OS-based efficacy testing. Soft tissue sarcomas (STS) comprise >70 WHO recognized subtypes with distinct biology, natural history, and treatment responsiveness. Incidence is low (U.S. ~3.4–3.5/100,000 per year), making large, subtype pure RCTs with OS power logistically prohibitive.[13] Bone sarcoma subtypes add further diversity (e.g., osteosarcoma, Ewing sarcoma) and are often studied using event free survival (EFS) as opposed to PFS or OS.[14]

Multimodality care and salvage dilute OS differences. Surgery and radiation therapy are integral across the disease continuum with outcomes dependent, in part, on how those interventions were ordered and the expertise of the clinical and surgical team. Moreover, multiple post-protocol therapies (cytotoxic regimens, tyrosine kinase inhibitors (TKIs) in Gastrointestinal Stromal Tumors (GIST), emerging immunotherapies or targeted agents in select subtypes) attenuate between-arm OS differences.[15] As FDA acknowledges in the draft guidance, ethically required crossover further impacts OS interpretation.

The clinical studies supporting FDA approvals in sarcoma underscore the importance of selecting efficacy endpoints based on the context of the specific condition, its patient population, and the studied treatment. Select examples include:

Pazopanib (Votrient) — adults with advanced soft-tissue sarcoma other than liposarcoma[16]

- PALETTE study enrolled 369 patients with multiple sarcoma subtypes and randomly assigned them 2:1 to pazopanib or placebo.

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[13] Spalato-Ceruso, M., Ghazzi, N.E. & Italiano, A. New strategies in soft tissue sarcoma treatment. *J Hematol Oncol* **17**, 76 (2024). https://doi.org/10.1186/s13045-024-01580-3

[14] Tanaka K, Kawano M, Iwasaki T, Itonaga I, Tsumura H. A meta-analytic evaluation of the correlation between event-free survival and overall survival in randomized controlled trials of newly diagnosed Ewing sarcoma. BMC Cancer. 2020 May 5;20(1):379. doi: 10.1186/s12885-020-06871-9. PMID: 32370741; PMCID: PMC7201711.

[15] Korn EL, Freidlin B, Abrams JS. Overall survival as the outcome for randomized clinical trials with effective subsequent therapies. J Clin Oncol. 2011 Jun 10;29(17):2439-42. doi: 10.1200/JCO.2011.34.6056. Epub 2011 May 9. PMID: 21555691; PMCID: PMC3107757.

[16] van der Graaf WT, Blay JY, et al., Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012 May 19;379(9829):1879-86. doi: 10.1016/S0140-6736(12)60651-5. Epub 2012 May 16. PMID: 22595799.

- Participants progressing on placebo received post-protocol treatment
- The primary endpoint was PFS
- The study found:
  - Pazopanib improved PFS (about 4.6 months vs 1.6 months).
  - OS was similar between groups, potentially due to effective post-protocol treatment.
- QoL was maintained in the pazopanib group
- *In mixed sarcoma groups where later treatments are used, PFS shows benefit earlier and more clearly than OS.*

Trabectedin (Yondelis) -- adults with liposarcoma or leiomyosarcoma who have been treated with anthracycline[17]

- Study enrolled 518 people and randomly assigned them 2:1 to trabectedin or dacarbazine.
- OS was the primary endpoint; PFS and symptom control were also measured.
- The study found:
  - Trabectedin improved PFS (about 4.2 months vs 1.5 months).
  - OS was similar (12-13 months)
  - Patients receiving trabectedin had a longer time to first opioid, suggesting improved symptom control.
- *PFS and symptom control may better reflect benefit than OS.*

Eribulin (Halaven) -- adults with liposarcoma (trial also enrolled leiomyosarcoma)[18]

- Study enrolled 452 people and randomly assigned them 1:1 to eribulin or dacarbazine.
- The primary endpoint was OS.
- The study found:
  - OS improved with eribulin (about 13.5 months vs 11.5 months).
  - The OS benefit was driven by those with liposarcoma (about 15.6 months vs 8.4 months).
  - Leiomyosarcoma patients did not have improved OS with eribulin
  - PFS was similar between groups.
  - Quality-of-life scores were generally maintained.

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[17] Demetri GD, von Mehren M, et al., Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol. 2016 Mar 10;34(8):786-93. doi: 10.1200/JCO.2015.62.4734. Epub 2015 Sep 14. PMID: 26371143; PMCID: PMC5070559.

[18] Osgood CL, Chuk MK, Theoret MR, Huang L, He K, Her L, Keegan P, Pazdur R. FDA Approval Summary: Eribulin for Patients with Unresectable or Metastatic Liposarcoma Who Have Received a Prior Anthracycline-Containing Regimen. Clin Cancer Res. 2017 Nov 1;23(21):6384-6389. doi: 10.1158/1078-0432.CCR-16-2422. Epub 2017 Feb 27. PMID: 28242632; PMCID: PMC10182892.

- *Pooling different sarcoma types can blur subtype distinctions on OS. FDA limited the label to liposarcoma.*

Imatinib (Gleevec/Imkeldi) adults with gastrointestinal stromal tumor (GIST)[19] and adults with dermatofibrosarcoma protuberans (DFSP)[20]

- For GIST, randomized studies used PFS as primary endpoint; crossover was permitted
- For DFSP (a very rare skin-related sarcoma), tumor response rates were assessed from small single-arm studies.
- The studies found:
    - In GIST, imatinib clearly delayed tumor growth, but OS was hard to interpret due to crossover.
    - In DFSP, a benefit was observed in reduced tumor size
- *Efficacy targets are context dependent - PFS with ethical crossover in GIST, and tumor response in ultra-rare DFSP.*

Regorafenib (Stivarga) adults with GIST after imatinib and sunitinib have stopped working[21]

- The GRID study enrolled 199 patients and randomly assigned them 2:1 to regorafenib or placebo.
- Crossover was permitted; 85% of patients on placebo crossed over to regorafenib
- PFS was the primary endpoint
- The study found:
    - A PFS benefit in the Regorafenib group (4.8 months vs 0.9 months).
    - OS did not demonstrate statistically significant difference in intention-to-treat population due to crossover.
    - QoL measures suggested slower functional decline with regorafenib.
- *When crossover is ethically required, PFS and patient-reported outcomes tell the benefit story; OS is not a clean efficacy measure.*

[19] Chiang KC, Chen TW, et al., Advanced gastrointestinal stromal tumor patients with complete response after treatment with imatinib mesylate. World J Gastroenterol. 2006 Apr 7;12(13):2060-4. doi: 10.3748/wjg.v12.i13.2060. PMID: 16610057; PMCID: PMC4087685.
[20] Rutkowski P, Van Glabbeke M, et al., Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. J Clin Oncol. 2010 Apr 1;28(10):1772-9. doi: 10.1200/JCO.2009.25.7899. Epub 2010 Mar 1. PMID: 20194851; PMCID: PMC3040044.
[21] Ferraro D, Zalcberg J. Regorafenib in gastrointestinal stromal tumors: clinical evidence and place in therapy. Ther Adv Med Oncol. 2014 Sep;6(5):222-8. doi: 10.1177/1758834014544892. PMID: 25342989; PMCID: PMC4206614.

Ripretinib (Qinlock) — adults with GIST after three or more prior therapies (late-line use)[22]

- The INVICTUS study enrolled 129 patients, randomly assigned 2:1 to ripretinib or placebo.
- Crossover from placebo to ripretinib was allowed
- PFS was the primary endpoint; QoL data was collected
- The study found:
    - Ripretinib improved PFS (6.3 months vs 1.0 months).
    - Patients in the ripretinib arm maintained quality of life longer than those on placebo
    - OS data favored ripretinib against placebo, but crossover complicated a clean OS comparison.
- *In late-line GIST with crossover and multiple prior treatments, PFS and preserved quality of life are the most reliable signals of benefit.*

Ultra-rare subtype treatments were approved based on overall response rate and durability of response. Examples include:

- **Tazemetostat** for epithelioid sarcoma[23] and **sirolimus protein-bound nanoparticles (nabsirolimus)** for PEComa[24] received approval/accelerated approval based on overall response rate (ORR) in single arm studies.
    - Continued access to this treatment is contingent on successful completion of a confirmatory study.
    - SFA is concerned that approval for this treatment (the only option for people diagnosed with epithelioid sarcoma) is in jeopardy as recruiting patients from a small population to an RCT when the therapy is already available poses insurmountable barriers to fulfilling regulatory requirements for traditional approval.

- **Atezolizumab** for alveolar softpart sarcoma (ASPS) similarly leveraged response-based evidence in a rare pediatric inclusive population.[25]

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[22] Kumar V, Doros L, et al., FDA Approval Summary: Ripretinib for Advanced Gastrointestinal Stromal Tumor. Clin Cancer Res. 2023 Jun 1;29(11):2020-2024. doi: 10.1158/1078-0432.CCR-22-2400. PMID: 36485007; PMCID: PMC10238554.

[23] Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study - The Lancet Oncology

[24] Wagner AJ, Ravi V, et al., *nab*-Sirolimus for Patients With Malignant Perivascular Epithelioid Cell Tumors. J Clin Oncol. 2021 Nov 20;39(33):3660-3670. doi: 10.1200/JCO.21.01728. Epub 2021 Oct 12. Erratum in: J Clin Oncol. 2023 Dec 10;41(35):5477. doi: 10.1200/JCO.23.02173. PMID: 34637337; PMCID: PMC8601264.

[25] Chen AP, Sharon E, et al., Atezolizumab for Advanced Alveolar Soft Part Sarcoma. N Engl J Med. 2023 Sep 7;389(10):911-921. doi: 10.1056/NEJMoa2303383. PMID: 37672694; PMCID: PMC10729808.

Sarcoma trials have routinely and appropriately relied on PFS/EFS, ORR, and DOR as primary endpoints, while OS is collected and interpreted with caution due to crossover, salvage, and small/heterogeneous populations.

(2) FDA should harmonize the draft guidance with prior (final) guidance on multiple endpoints.

In rare, heterogeneous diseases such as sarcoma, OS is typically underpowered and slow to mature making it impossible to reliably assess OS without extending studies beyond the upper boundaries of acceptable clinical study duration (in extremely, very heterogenous conditions, OS data can take decades to mature). Multiplicity concerns can mislead stakeholders and regulators if non-significance is interpreted as "no benefit" rather than "not enough events yet." FDA's Multiple Endpoints guidance cautions against drawing efficacy conclusions from secondary endpoints without appropriate alpha control. This is a recurrent problem when OS is listed as an efficacy endpoint, but trials are not designed (and potentially cannot be designed) to detect an OS difference.

We urge FDA to finalize the draft guidance to incorporate and maintain consistency with previously issued guidance to industry. This can be done without compromising the safety goals of the draft guidance by acknowledging that OS data be collected and analyzed to detect harms with pre-specified thresholds and follow-up beyond the study's duration.

(3) **SFA urges FDA to clarify expectations for crossover in ethically sensitive settings**

SFA was disappointed with FDA's inclusion of cautionary language suggesting that crossover be limited and implying that study sponsors must justify inclusion of protocol-specified crossover. Sarcoma patients have few treatment options and often participate in multiple clinical trials over the course of their disease, consistent with NCCN recommendations on the clinical trial setting as potentially the "best" treatment option. Patients progressing on either arm of a clinical trial are entitled to the best care available if their cancer progresses – whether that is achieved through crossover, enrollment in a different study, or salvage therapy. Any post-protocol treatment presents risks of confounding OS data unless the patient population is of sufficient size to dilute the impact of that uncontrolled variable.[26]

In sarcoma studies, crossover is common in both first line and more advanced disease; absent protocol-specified crossover, participants in both study arms can and do seek additional care when their cancer progresses. The statement suggesting limited use of crossover in cancer

[26] See, e.g., Zietemann VD, Schuster T, Duell TH. Post-study therapy as a source of confounding in survival analysis of first-line studies in patients with advanced non-small-cell lung cancer. J Thorac Dis. 2011 Jun;3(2):88-98. doi: 10.3978/j.issn.2072-1439.2010.12.07. PMID: 22263071; PMCID: PMC3256510.

studies implies a prioritization of "clean" data over patient lives that we suspect FDA did not intend. We strongly urge FDA to focus on strategies to account for crossover and salvage therapies rather than cautioning against permitting access to study drug among participants randomized to the control arm of an RCT.

(4) Sarcoma patients without FDA-approved treatment options often rely on older, cytotoxic treatment regimens that impact QoL and can lead to future health concerns. We strongly urge FDA to incorporate into its guidance a recommendation for sponsors to include patient-centered endpoints that can signal treatment benefit and harms.

Legacy cytotoxics remain central in many sarcoma subtypes and are associated with reduced quality of life and potential short- and long-term harms. The table below provides an illustrative set of sarcoma subtypes, the systemic therapy commonly used, and toxicities associated with those treatments.

Table 1: Sarcoma subtypes for which QoL and disease/treatment burden are particularly relevant

Sarcoma	Usual systemic therapy	Modern on-label options?	Key toxicities/QoL impact	Unmet-need
Undifferentiated Pleomorphic Sarcoma (UPS)/ Myxofibrosarcoma	Doxorubicin ± ifosfamide; gem/docetaxel; ± pazopanib	Few histology-specific labels	Cardiotoxicity; ifosfamide encephalopathy/ nephrotoxicity; fatigue/myelosuppression	Old chemo with modest disease control; OS rarely clean
Leiomyosarcoma (LMS)	Dox/IFO; gem/docetaxel; trabectedin; pazopanib	Trabectedin; Pazopanib	Chemo toxicities; hepatic AEs (trabectedin); chronic TKI AEs	Chemo backbone persists; PROs critical
Liposarcoma (LPS)	Dox/IFO; eribulin; trabectedin	Eribulin (LPS); Trabectedin (LPS/LMS)	Cardiac/neuro/nephro; fatigue	Subtype-specific activity; many patients are still treated by cycling older chemo
Angiosarcoma	Weekly paclitaxel; anthracyclines; TKIs variably	—	Neuropathy/fatigue; cardiotoxicity	Chemo dependence persists; QoL matters
MPNST	Dox ± IFO	—	Chemo toxicities; high relapse	Old chemo with limited benefit; trials needed
Chondrosarcoma (conv.)	Surgery ± radiation; systemic chemo limited	—	Functional loss from surgery/Radiation	Systemic options scarce

Osteosarcoma (ped/AYA)	MAP ± IFO	—	Cardiac, ototoxicity, renal, fertility, neurocognitive	Stagnant outcomes esp. in metastatic/ relapsed disease
Ewing (ped/AYA)	VDC/IE	—	Cardiac/infertility; RT late effects	Relapse OS <20–30%
Rhabdomyosarcoma (ped.)	VAC/IVA	—	Chemo+RT late effects	High-risk; relapse outcomes poor
DSRCT (AYA)	P6 + aggressive local therapies	—	Very heavy acute/late toxicity	5-y OS often ≤15–25%

The recently discontinued R&D efforts to offer patients with dedifferentiated liposarcoma an alternative to doxorubicin illustrates the complexities associated with first-line sarcoma treatment studies relying on a single, pre-defined endpoint within a randomized "superiority" design. Boehringer Ingelheim conducted a randomized trial comparing brigimadlin to doxorubicin with a primary endpoint of PFS by blinded central review and protocol-specified crossover from doxorubicin to brigimadlin at progression. The study incorporated patient-reported outcomes/HRQoL per the statistical plan.

Peer-reviewed summaries reported that the primary PFS endpoint was not met (HR 0.79; median PFS 8.4 vs 7.2 months), but improvements were observed in both objective response rate (ORR) 33 (22.3) vs 14 (8.6) and disease control 128 (86.5) 117 (72.2). The hierarchical testing strategy precluded any formal claims on objective response or disease control, and OS data was immature and likely confounded by protocol-specified crossover, making it unsuitable as an efficacy endpoint. For sarcoma patients, brigimadlin appeared to offer at least comparable efficacy to doxorubicin and a manageable side effect profile, particularly when compared to the long-term effects seen with doxorubicin. It also offered quality of life advantages and a reduced treatment burden given the method of delivery (as noted, sarcoma patients often travel long distances to access expert care). It is, however, unlikely that the benefits conferred to patients due to brigimadlin's more favorable safety profile would have translated into a statistically significant OS advantage.

Similarly, the systemic regimens for osteosarcoma, Ewing sarcoma, rhabdomyosarcoma (RMS), and DSRCT have changed little in decades and are associated with substantial late-effect burdens (cardiac, ototoxic, renal, endocrine/fertility, neurocognitive). Survival has remained stagnant in metastatic/relapsed osteosarcoma. Relapsed Ewing and high-risk/relapsed RMS have poor outcomes. The 5-year survival for DSRCT is often≤15–25%. These sarcomas are often found in children, adolescents and young adults. Given the lifelong side effects associated with existing treatments, combined with their impact on QoL, there is a particularly urgent unmet need for targeted therapies to improve both prognosis and quality of life for these young cancer patients. Although tracking OS for safety may be helpful in assessing harms, incorporating endpoints such

as limb function, pain, and core patient reported outcomes (PROs) will enable sponsors to detect potential harms earlier than relying exclusively on OS data. While this is a crucial consideration for sarcomas impacting children and young adults, patient-centered outcomes are relevant (and important) for all sarcoma patients and should be considered by sponsors studying any cancer.

The table below identifies instruments for collecting PROs and health-related QoL (HRQoL) data in the sarcoma patient population.

Table 2: Instruments for collecting PRO and HRQoL data in sarcoma studies

Instrument	What it measures	Burden	Interpretation anchors	Used in trials	How to deploy in R&D
EORTC QLQ-C30[27]	Global QoL; function; symptoms	~30 items	10-point rule; scale-specific MIDs available	PALETTE; INVICTUS; INTRIGUE	Make Physical & Role Function key secondaries; TUDD & responder analyses
EQ-5D-5L[28]	Utility/QALY; VAS	5 items + VAS	Utility change; QALY impact	PALETTE; INVICTUS	Include for health-economics; show utility preserved alongside PFS
PRO-CTCAE[29]	Symptomatic AEs (freq/sev/ interference)	Modular; adult + pediatric	Responder definitions; time-to-worsening	Increasingly embedded	Select 10–15 items (fatigue, neuropathy, HFS); weekly early cycles; power a safety secondary
PROMIS (PF, Pain Interference)[30]	Function; symptom burden	Short forms/CAT	2–6 T-score points (group change)	Broad oncology	Use when limb/organ function central; prespecify responder thresholds
Sarcoma-specific tools (e.g., SAM;[31] SAM-Paeds)[32]	Sarcoma-specifi c concerns	~22 items; emerging	Exploratory until fully validated	Pilots underway	Use alongside core PROs; label as exploratory

[27] EORTC Quality of Life website | EORTC Quality of Life Group website
[28] EQ-5D-5L - EuroQol
[29] Overview of the PRO-CTCAE
[30] PROMIS_Pain_Interference_Scoring_Manual.pdf
[31] The Sarcoma Assessment Measure (SAM): Preliminary Psychometric Validation of a Novel Patient-Reported Outcome Measure
[32] Taylor RM, Purnell SA, et al., Sarcoma Assessment Measure-Paediatric Version (SAM-Paeds): development of a disease-specific patient reported outcome measure for children with sarcoma. J Patient Rep Outcomes. 2025 Mar 11;9(1):30. doi: 10.1186/s41687-025-00857-6. PMID: 40067547; PMCID: PMC11896951.

Conclusion

SFA appreciates FDA's focus on patient protection and regulatory clarity. In sarcoma, requiring OS as an efficacy endpoint (primary or alpha-controlled secondary) will often delay decisions or mislead stakeholders due to underpowered, diluted comparisons—while adding little to the benefit-risk assessment. FDA's concerns related to treatment harms can be effectively and efficiently addressed without reducing the practical feasibility of sarcoma R&D programs if study sponsors:

- Collect FDA Core PROs[33] (physical and role function, disease symptoms, symptomatic AEs/overall side-effect impact); then add sarcoma-specific modules where validated.
- Prespecify analysis sets, time points, intercurrent-event handling; allocate alpha for key PRO endpoints where pivotal.
- Match cadence to toxicity: frequent early PRO-CTCAE; monthly QLQ-C30 thereafter; maintain collection post-treatment to capture persistent effects.
- Pair PFS/EFS/ORR+DOR + PROs for efficacy; track OS for safety with independent Data Monitoring Committee (DMC) and harm thresholds.
- Reduce missingness with ePROs (BYOD/tablet), ≤15-minute burden per visit, reminders during critical windows.

SFA believes the draft guidance's framework for pre-specifying OS for safety in sarcoma studies can reliably inform study sponsors, FDA, clinicians and patients on the benefit/risk balance. The approach focuses on what matters most to patients - slowed or halted progression, preserved function, and lower symptomatic burden.

Once again, SFA thanks the FDA for this opportunity to comment on its draft guidance. We remain eager to collaborate with FDA toward our shared goal of facilitating innovation while ensuring that patients are not harmed by ineffective or unsafe treatments. If you have any questions or need additional information, please contact Brandi Felser at bfelser@curesarcoma.org.

Respectfully,

Brandi Felser
Chief Executive Officer

Mark Thornton, MD, PhD
President

[33] Core Patient-Reported Outcomes in Cancer Clinical Trials Final Guidance for Industry